Factors Associated With Loss of Penicillin G Concentrations in Serum After Intramuscular Benzathine Penicillin G Injection: A Meta-analysis

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14. ABSTRACT

Benzathine penicillin G (pen G) is prescribed for treatment and prophylaxis against conditions due to group A streptococcus. The World Health Organization recommends secondary prophylaxis at 3- and 4-week intervals depending on the patient???s age and health status. Studies were reviewed for the persistence of serum pen G over the course of 4 weeks after intramuscular injection. Published literature from the PubMed database was reviewed. Thirty-four data sets were analyzed for serum pen G concentration over time. The data were analyzed by (1) survival probability estimates of pen G levels above minimum protective over the course of 4 weeks using a Kaplan-Meier model, and (2) analysis of variance of mean pen G levels over time, including as factors date of publication and health and age of subjects. Weighted mean serum levels across studies were below 0.02 ??g/ml before 3 weeks. Mean serum pen G concentration decay rates were higher, and the percentage of subjects with serum pen G above minimum protective levels were found to decrease significantly faster in studies performed (1) with healthy subjects than in studies with sick subjects, (2) after 1978 than in studies done before, and (3) with adults than in studies with children. Exponential modeling of percentages of subjects above minimum protective shows that approximately 65% of subjects were above minimum protective levels at 3 weeks and approximately 45% at 4 weeks. Recommendations for prophylaxis should be re-evaluated, with further study of serum pen G levels and dose response in specific target populations.

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Factors Associated With Loss of Penicillin G Concentrations in Serum After Intramuscular Benzathine Penicillin G Injection: A Meta-analysis

Michael P. Broderick, PhD, Christian J. Hansen, BS,* and Dennis J. Faix, MD†*

Background: An interval of 3–4 weeks between intramuscular injections of 1.2 million units of benzathine penicillin G as prophylaxis against group A streptococcal infection is recommended by health organizations for patients with pediatric rheumatic fever and heart disease.

Methods: We reviewed the literature for evidence of the persistence of serum penicillin G during the first 4 weeks after the recommended dose of benzathine penicillin G.

Results: The weighted-mean concentration was <0.02 μg/mL by 3 weeks after the initial dose. Weighted means were lower in studies done after 1990 than before ($P < 0.01$), in studies dealing with secondary versus primary prophylaxis ($P < 0.01$) and in studies in children versus those in adults ($P < 0.02$).

Conclusions: Recommendations for benzathine penicillin G prophylaxis may need reevaluation.

Key Words: benzathine penicillin G, group A streptococcus, prophylaxis, meta-analysis, systematic review

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In the late 1940s, studies[1–4] reported success in treating and preventing rheumatic fever with penicillin. Benzathine penicillin G (BPG) was introduced for prophylaxis against group A streptococcus (GAS) soon thereafter.[1] In 1952, Stollerman and Rusoff[2] tested different dosing regimens on serum penicillin G (pen G) concentrations over time. As a result of these and subsequent studies,[3–6] intramuscular injection of 1.2 million units (MU) of BPG every 4 weeks was established as a standard. Several official guidelines recommend a 3- to 4-week schedule using a 1.2 MU injection.[7–10] Nevertheless, literature reviews suggest there are concerns regarding the appropriate frequency of prophylaxis with BPG.[11,12]

Studies have observed various GAS illness rates during secondary prophylaxis regimens and with various serum pen G concentrations after intramuscular administration (eg, [12–16]). On the basis of several studies, Kaplan et al[12,17,18] argued that the current protective effects of BPG are unclear or diminished (see also Ayoub).[11]

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A range of minimum-protective serum pen G concentrations against GAS has been proposed based on pen G's minimum inhibitory concentration (MIC).[11] Estimated MICs have been reported from 0.007[14] to 0.03[13,19] μg/mL, with one reference reporting MIC^{50} as 0.01 and MIC^{90} as 0.03.[20] Kaplan et al[21] chose 0.02 μg/mL as the minimum-protective serum value of pen G based on findings that showed that the vast majority of GAS strains are susceptible to concentrations lower than 0.02 μg/mL.

The rapid decline of serum pen G seen in specific populations[22,23] emphasizes the need for monitoring the relationship between serum pen G concentrations and time after administration. We provide a meta-analysis examining available literature on serum pen G persistence and estimates of the time from parenteral administration of 1.2 MU of benzathine pen G until a minimum-protective concentration is lost for (1) mean serum values and (2) a threshold percentage of study subjects.

METHODS

Search Strategy

Several reference collections such as Biomedical Reference Collection were queried for relevant terms such as "benzathine penicillin." The reference sections of the articles produced by these queries were inspected for additional studies suitable for inclusion.

Study Selection

Measures evaluated included (1) mean serum pen G concentrations and (2) the percentage of subjects whose pen G was above minimum-protective values of 0.01, 0.02 or 0.03 μg/mL, measured at day 1, and 1, 2, 3 and 4 weeks after the initial dose. Studies in which 1.2 MU of BPG were administered intramuscularly were evaluated. From the 1950s through the 1990s, the standard technique for measuring pen G serum concentrations was a diffusion assay. This technique was used by all of the studies but one,[24] which used liquid chromatograph mass spectrometry. Each study was blinded and independently evaluated by the authors on 5 categories of quality assessment.

Data Analysis

Descriptive statistics of measures at each time point for each study and percentages of subjects above the minimum detectable values were extracted. Separate studies within an article were distinguished. Age ranges, the assay method, minimum concentration of detection of serum pen G, the year of the study and whether the BPG was for primary or secondary prophylaxis, were noted. Pen G measurements were categorized as occurring at day 1, and at weeks 1, 2, 3 and 4 after the initial BPG dose.

Each study was weighted by multiplying its quality evaluation score by its sample size at each time point. The studies provided 2 types of data: (1) sample means of serum pen G, and/or (2) percentages of subjects having serum pen G values above a stated minimum-protective concentration. Analyses of variance (ANOVAs) were done on the weighted means for 3 divisions of

the studies: prophylaxis regimen (primary or secondary), period of study publication (pre-1990 or post-1990) and age range of subjects (children or adults). In each ANOVA, time point was also a factor. This was done likewise for the percentages above the minimum-protective concentrations. Half-lives of pen G concentrations were determined by exponential regression for each study and across studies, and for the age, health status and study-period divisions.

RESULTS

Twenty-seven articles reporting 37 studies were included in the analysis[2,3,5,6,14,21,22,24–43] (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B128).

Each study had measures occurring within 2 days of at least 1 of the 5 time points (day 1, week 1, week 2, week 3 and week 4; Table, Supplemental Digital Content 2, http://links.lww.com/INF/B129).

Rationales for inclusion of data from the studies are noted in Table, Supplemental Digital Content 2, http://links.lww.com/INF/B129. Quality evaluation scores ranged from 3 to 15 (mean = 13); studies scoring less than 12 were eliminated.

Decrease in Serum Pen G

There was an exponential decrease over time in the mean serum pen G concentration across studies (Fig., Supplemental Digital Content 3, http://links.lww.com/INF/B130). The exponential model estimated that at 3 weeks, the mean concentration was 0.015 μg/mL. Of the 24 studies (excluding Oran et al)[24] with data at 18–21 days, 12 had mean serum pen G values lower than the minimum-protective concentration of 0.02 μg/mL, and at days 28–30, 17 of the 21 studies were at or below 0.02 μg/mL.

Decrease in Percentage of Subjects Above Minimum-protective Serum Pen G

Twenty-nine studies reported percentages of subjects above 0.01, 0.02, and/or 0.03 μg/mL (Fig., Supplemental Digital Content 3, http://links.lww.com/INF/B130). In the 20 studies with data at 18–21 days, there were 9 in which ≥50% of the subjects had concentrations <0.02 μg/mL. This was also the case in 12 of the 19 studies with data at 28–30 days. The weighted means showed percentages of subjects below 0.01, 0.02, and 0.03 μg/mL at week 3 as 42%, 53,%, and 82%, respectively.

Categories of Subject and Study Characteristics

The ANOVAs of mean concentrations identified significant differences for each of the 3 factors: studies pre-1990 had consistently higher mean penicillin concentrations at each time point than studies post-1990 ($P < 0.001$; Fig. 1). Studies on secondary prophylaxis had consistently higher mean penicillin concentrations at each time point than did studies on primary prophylaxis ($P = 0.002$; Fig. 1). Studies evaluating children had consistently higher mean penicillin concentrations at each time point than did studies evaluating adults ($P = 0.018$; Fig. 1). However, in an ANOVA combining the 3 categories of studies, there was an interaction between age and prophylaxis ($P = 0.002$; there was only 1 study on children with primary prophylaxis).

The same data trends were seen for percentages above each of the 3 putative minimum-protective concentrations. Most of the ANOVAs were significant for the 3 factors. Children versus adults was only significant for the 0.01 μg/mL concentration.

The half-life of weighted-mean serum pen G concentration across studies was 1.15 weeks. Although within each of the factors the differences were not significant, the half-lives were shorter for post-1990 studies, primary prophylaxis and adults.

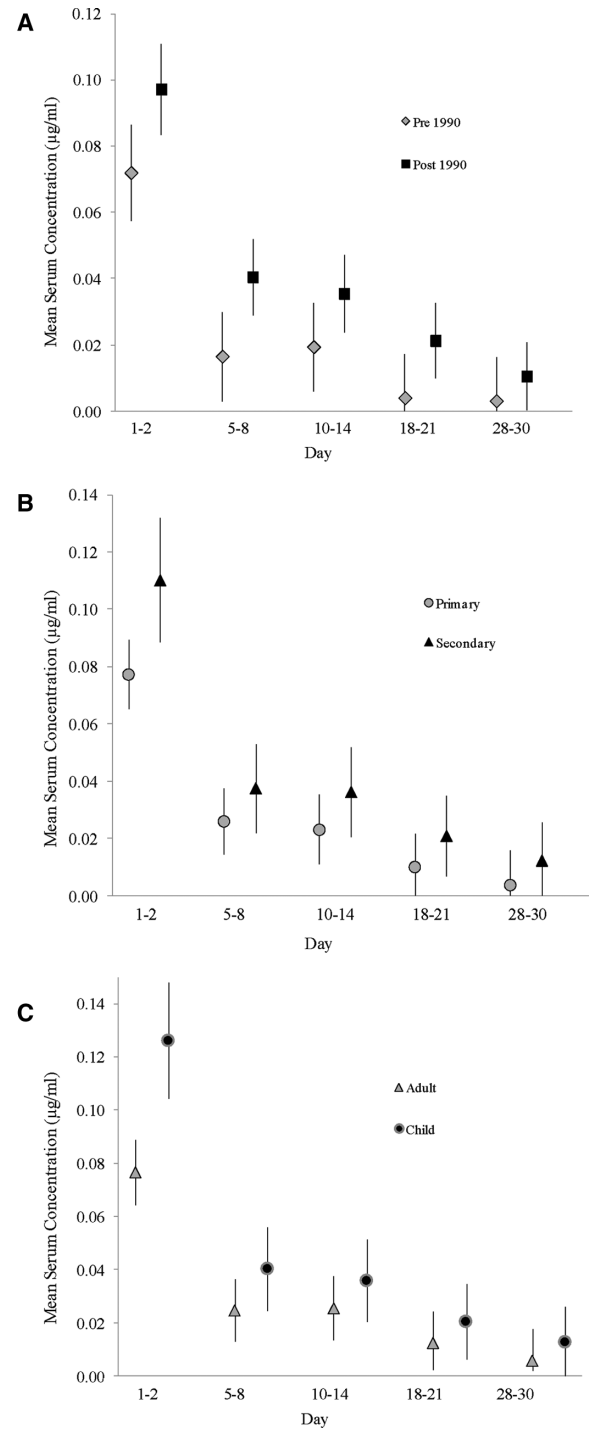

FIGURE 1. Categorization of studies. Panel A) Mean concentrations of studies before or after 1990. Panel B) studies on secondary versus primary prophylaxis. Panel C) studies on children versus adults. ANOVAs show the concentrations of each of these factors to be significantly different.

Laboratory methodologies were similar across studies (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B128). The studies inconsistently reported the variance at each time point. Therefore, we were unable to evaluate heterogeneity.

DISCUSSION

The mean pen G serum concentration and the percentage of subjects above the minimum-protective value varied by (1) prophylaxis regimen, with primary prophylaxis showing shorter duration of protection than secondary prophylaxis, (2) the time frame of study publication, with studies performed after 1990 demonstrating significantly shorter duration of protection than studies performed before 1990, and (3) the age range of patients/subjects, with significantly shorter durations for adults than for children. Prophylaxis and age were confounded, however.

Recommendations for successive doses of BPG are based upon an expectation that pen G concentrations drop below minimum-protective values between 3 and 4 weeks.[7,9,10] The meta-analysis showed that this expectation depends greatly on the protective value chosen. For example, in the exponential model the serum G concentration at 3 weeks was less than 0.02 μg/mL, and a large percentage of the subjects were unprotected at each of the 3 putative protective serum pen G levels.

By 3 weeks in post-1990 studies, the model's value was only 0.004 μg/mL (Fig. 1). Changes in formulation or manufacturing is a possible explanation for the difference in findings between pre-1990 and post-1990.[21] Supporting this explanation is one study's finding of a difference between pen G from 2 different manufacturers;[38] such differences could be correlated with shorter half-lives and/or lower initial serum concentrations.

The higher pen G concentrations seen in secondary prophylaxis regimens could be partly due to the primary prophylaxis group being composed mostly of healthy individuals, who might be more active and metabolize pen G faster than the individuals comprising the secondary prophylaxis group. The evidence for this is unclear: one study found that activity level has no effect on pen G persistence,[39] another that the loss of pen G was precipitous in healthy and active military recruits.[22] A second possibility for the greater pen G persistence in secondary prophylaxis is that whereas studies of primary prophylaxis generally involved only a single dose of BPG, studies of secondary prophylaxis generally involved multiple doses, which may produce longer-term low-concentration intramuscular depots of drug (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/B128).

The argument that faster metabolism could account for the differences seen in prophylaxis regimen would seem to be contradicted by the finding that adults eliminate pen G faster than children. However, most of the adults received primary prophylaxis and most of the children secondary, confounding the 2 factors. It may be that the effect seen in children versus adults is a function of prophylaxis.

The remarkable variation in pen G half-lives in individual studies (Fig., Supplemental Digital Content 3, http://links.lww.com/INF/B130) attests to large differences in the pharmacokinetics of BPG (if not the conduct, laboratory procedures or data analyses of the studies). The only other study to have measured the half-life of serum pen G concentrations[44] found, as the meta-analysis did, that concentrations were halved within 10 days. This is not a concern as long as initial concentrations are sufficiently high. However, the interaction of absolute concentration and half-life is apparently driving concentrations to potentially nonprotective values in less than 3 weeks. Subjects who begin with relatively low concentrations may become unprotected faster than expected.

The World Health Organization recommendations refer to "high-risk" and "low-risk" populations, and caution that many factors should be taken into account. For patients <27 kg (the median for those aged 8.5 years), 0.6 MU is recommended,[9] although 0.6 MU has been found inadequate for such individuals.[28,31] Some studies we analyzed gave 1.2 MU to children regardless of weight,[14,30] and interaction between age, height, weight or body surface area was inconsistently reported.[22,26] Specific populations were clearly not adequately covered by 4-week nor even 3-week intervals. Serum pen G concentrations in healthy adult prisoners or the military were likely inadequate after 2 weeks.[22,37] On the other hand, the meta-analysis showed that those receiving secondary BPG prophylaxis tended to maintain adequate serum pen G concentrations for up to 3 or 4 weeks.

The relationship between laboratory-defined MICs and the biologically relevant minimum-protective serum pen G concentration is not well-defined, as evidenced by the different target values discussed in the literature. Disease rates among those receiving BPG treatment suggest MICs may overestimate minimum-protective concentrations.[11,29] The majority of GAS strains are susceptible to lower concentrations of penicillin than implied by minimum-protective values.[21] Urine excretion of pen G continues for considerably longer than 4 weeks, suggesting pen G may still be present,[37] though below the minimum detectable serum concentration.

Expectations of protection should vary according to factors such as those presented here. Given the diminished persistence seen in post-1990 studies, recommendations based on older studies may need to be reconsidered.

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